

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: James Ronald Lawter and Stephen J. Comiskey

Serial No.: Continuation of 09/661,836

Express Mail Label
No. EL 639 985 041 US

Filed: December 4, 2001

Date of Deposit: December 4, 2001

For: FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Box Patent Application
U.S. Patent and Trademark Office
P.O. Box 2327
Arlington, VA 22202

PRELIMINARY AMENDMENT

Sir:

Prior to examination, please amend the application as follows.

In the Specification

On page 1, after the title and before "Field of the Invention", please insert the following heading and paragraph.

--Cross-Reference to Related Applications

This application is a continuation of pending prior application U.S. Serial No. 09/661,836 filed September 14, 2000, which claims priority to U.S. Serial No. 60/153,892 filed September 14, 1999.--

On page 1, please delete lines 6-7.

In the Claims

1. (amended) A pharmaceutical composition [for treating or preventing mucositis] comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration [to the mucosa] of an effective amount of a tetracycline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered.

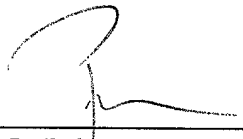
Remarks

Applicants have attached a marked-up version of page 1 of the Specification, and a clean copy of page 1 of the Specification with the changes incorporated.

Continuation of U.S.S.N. 09/661,836
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The claims have been amended to incorporate the limitations of claim 9 into the independent claims.

Respectfully submitted,



Patrea L. Pabst
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Date: December 4, 2001

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this paper and any documents referred to as attached or enclosed are being deposited with the United States Postal Service on this date, December 4, 2001, in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, Express Mail Label No. EL 639 985 041 US, addressed to Box Patent Application, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202.

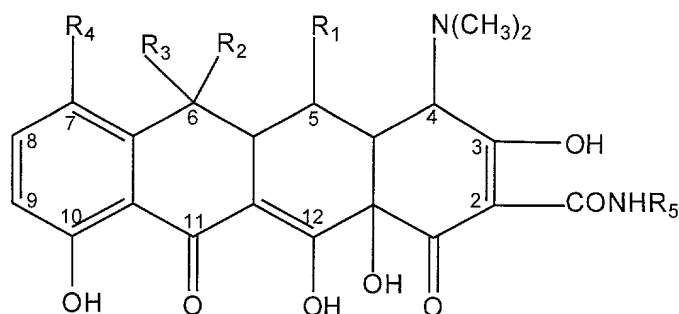


Pam Turnbough

Date: December 4, 2001

**Marked-Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)**

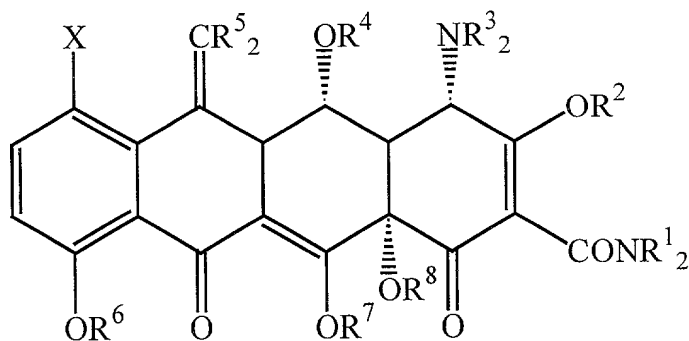
1. (amended) A pharmaceutical composition [for treating or preventing mucositis] comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

3. The composition of claim 2 wherein R₁ and R₂ are hydrogen or a hydroxyl group; R₃ is hydrogen or a methyl group; R₄ is a hydrogen atom, a halogen, or a nitrogen containing entity; and R₅ is a hydrogen atom, or nitrogen containing ring structure.

4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.
5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.
6. The composition of claim 2 having the following structure:



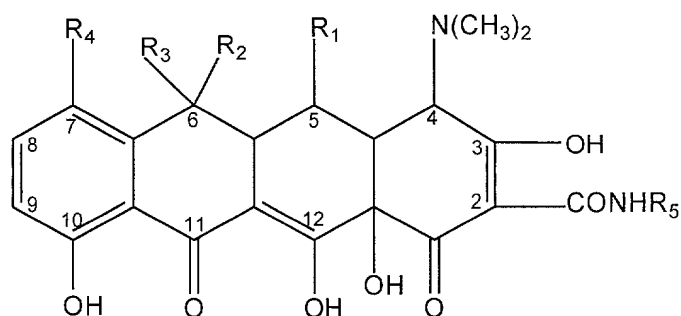
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are H; wherein R³ is CH₃; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.
9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.
10. The composition of claim 9 wherein the tetracycline is formulated as a dry powder.
11. The composition of claim 1 wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered to the mouth and then swallowed.
12. The composition of claim 8 wherein the tetracycline is in the form of a polyvalent metal ion complex.
13. The composition of claim 12 wherein the polyvalent metal ion is calcium or magnesium.
14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.
15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

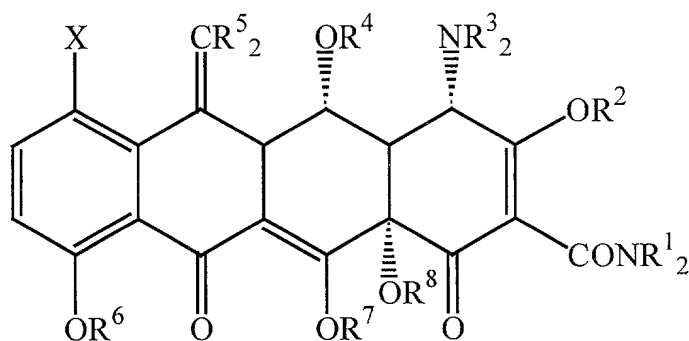
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R₁ and R₂ are hydrogen or a hydroxyl group; R₃ is hydrogen or a methyl group; R₄ is a hydrogen atom, a halogen, or a nitrogen containing entity and R₅ is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

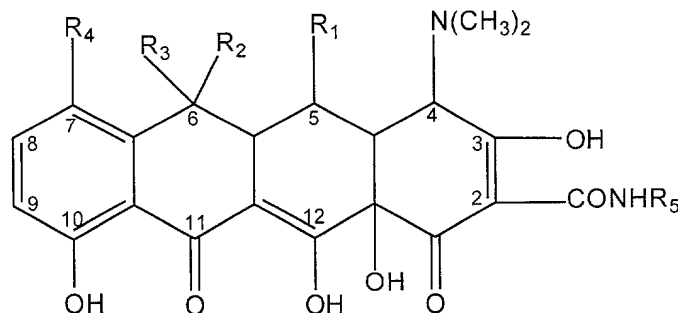
19. The method of claim 18 wherein the tetracycline is meclocycline,
 wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H;
 wherein R^3 is CH_3 ; and wherein X is a chloro group.

20. The method of claim 15 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

21. The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for administration of the tetracycline to the patient.
22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.
23. The method of claim 15 wherein the patient is treated between one and six times daily.
24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration [to the mucosa] of an effective amount of a tetracycline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered.

Clean Copy of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(i)

1. (amended) A pharmaceutical composition comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:

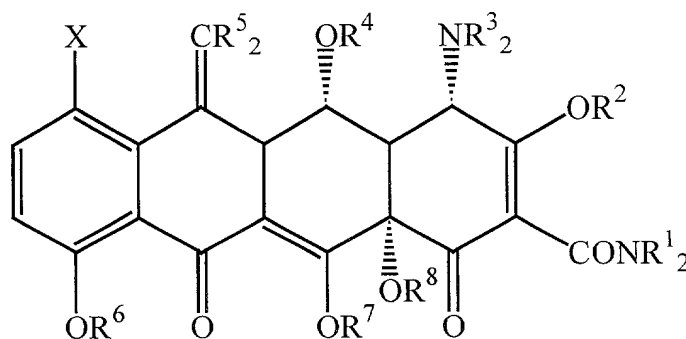


wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

3. The composition of claim 2 wherein R₁ and R₂ are hydrogen or a hydroxyl group; R₃ is hydrogen or a methyl group; R₄ is a hydrogen atom, a

halogen, or a nitrogen containing entity; and R_5 is a hydrogen atom, or nitrogen containing ring structure.

4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.
5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.
6. The composition of claim 2 having the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

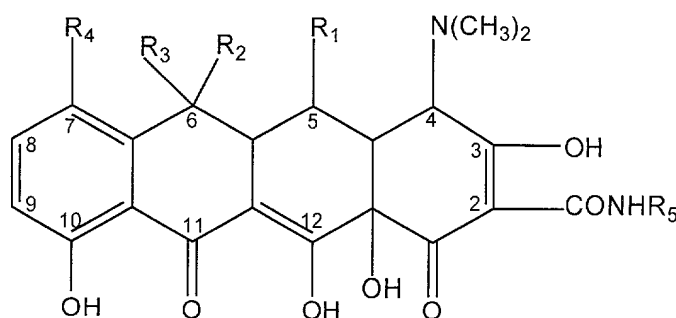
wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H;

wherein R^3 is CH_3 ; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.
9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.
10. The composition of claim 9 wherein the tetracycline is formulated as a dry powder.
11. The composition of claim 1 wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered to the mouth and then swallowed.
12. The composition of claim 8 wherein the tetracycline is in the form of a polyvalent metal ion complex.
13. The composition of claim 12 wherein the polyvalent metal ion is calcium or magnesium.
14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.
15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

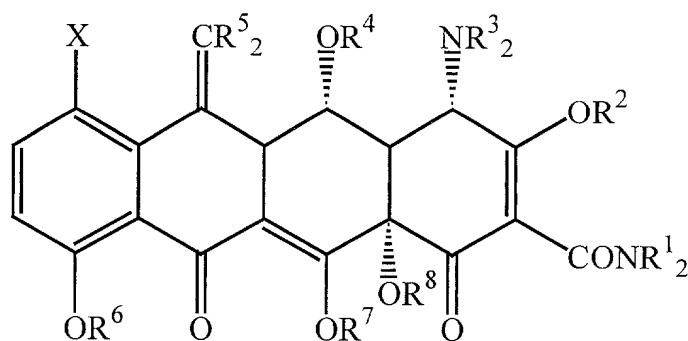
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R_1 - R_5 may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity and R_5 is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

19. The method of claim 18 wherein the tetracycline is meclocycline,

wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H;

wherein R^3 is CH_3 ; and wherein X is a chloro group.

20. The method of claim 15 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

21. The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for administration of the tetracycline to the patient.
22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.
23. The method of claim 15 wherein the patient is treated between one and six times daily.
24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration of an effective amount of a tetracycline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered.

項目	単位	数値
1. 総人口	人	1,234,567
2. 男性人口	人	612,345
3. 女性人口	人	622,222
4. 人口密度	人/平方キロメートル	123.45
5. 出生率	人/1,000人	10.5
6. 死亡率	人/1,000人	8.2
7. 自然増減率	人/1,000人	2.3
8. 平均寿命	歳	75.6
9. 識字率	%	98.7
10. 労働力人口	人	543,210
11. 失業率	%	4.5
12. 所得格差	指数	1.2
13. 環境指数	点	85.0
14. 教育指数	点	92.0
15. 健康指数	点	88.0
16. 経済成長率	%	3.5
17. 物価指数	点	105.0
18. 貿易収支	億ドル	12.3
19. 外国直接投資	億ドル	5.6
20. 政府債務	億ドル	150.0
21. 財政赤字	億ドル	10.0
22. 中央銀行資産	億ドル	200.0
23. 通貨供給量	億ドル	1,500.0
24. 消費者物価	%	2.0
25. 生産者物価	%	1.5
26. 実質GDP	億ドル	500.0
27. 名目GDP	億ドル	550.0
28. 労働生産性	ドル/人	1,000.0
29. 技術革新指数	点	70.0
30. 環境意識指数	点	65.0
31. 社会安定指数	点	80.0
32. 文化政策指数	点	75.0
33. 国際化指数	点	82.0
34. 持続可能性指数	点	78.0
35. 透明性指数	点	72.0
36. 腐敗指数	点	68.0
37. 政治自由指数	点	70.0
38. 言論自由指数	点	75.0
39. 宗教自由指数	点	70.0
40. 少数民族権利指数	点	65.0
41. 労働権利指数	点	70.0
42. 環境保護指数	点	75.0
43. 社会福祉指数	点	80.0
44. 教育機会指数	点	85.0
45. 健康サービス指数	点	80.0
46. 住宅安定指数	点	75.0
47. 食料安全保障指数	点	80.0
48. 水資源管理指数	点	75.0
49. 気候変動適応指数	点	70.0
50. 災害リスク管理指数	点	75.0
51. 防災意識指数	点	70.0
52. 防災訓練実施率	%	90.0
53. 防災物資備蓄率	%	85.0
54. 防災計画策定率	%	95.0
55. 防災意識調査実施率	%	90.0
56. 防災教育実施率	%	85.0
57. 防災情報伝達率	%	90.0
58. 防災意識向上率	%	10.0
59. 防災訓練参加率	%	80.0
60. 防災物資点検率	%	95.0
61. 防災計画見直し率	%	80.0
62. 防災意識調査実施回数	回	1.0
63. 防災教育実施回数	回	1.0
64. 防災情報伝達回数	回	1.0
65. 防災意識向上回数	回	1.0
66. 防災訓練参加回数	回	1.0
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68. 防災計画見直し回数	回	1.0
69. 防災意識調査実施年数	年	1.0
70. 防災教育実施年数	年	1.0
71. 防災情報伝達年数	年	1.0
72. 防災意識向上年数	年	1.0
73. 防災訓練参加年数	年	1.0
74. 防災物資点検年数	年	1.0
75. 防災計画見直し年数	年	1.0
76. 防災意識調査実施頻度	頻度	1.0
77. 防災教育実施頻度	頻度	1.0
78. 防災情報伝達頻度	頻度	1.0
79. 防災意識向上頻度	頻度	1.0
80. 防災訓練参加頻度	頻度	1.0
81. 防災物資点検頻度	頻度	1.0
82. 防災計画見直し頻度	頻度	1.0
83. 防災意識調査実施回数/年	回数/年	1.0
84. 防災教育実施回数/年	回数/年	1.0
85. 防災情報伝達回数/年	回数/年	1.0
86. 防災意識向上回数/年	回数/年	1.0
87. 防災訓練参加回数/年	回数/年	1.0
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90. 防災意識調査実施頻度/年	頻度/年	1.0
91. 防災教育実施頻度/年	頻度/年	1.0
92. 防災情報伝達頻度/年	頻度/年	1.0
93. 防災意識向上頻度/年	頻度/年	1.0
94. 防災訓練参加頻度/年	頻度/年	1.0
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96. 防災計画見直し頻度/年	頻度/年	1.0
97. 防災意識調査実施回数/頻度	回数/頻度	1.0
98. 防災教育実施回数/頻度	回数/頻度	1.0
99. 防災情報伝達回数/頻度	回数/頻度	1.0
100. 防災意識向上回数/頻度	回数/頻度	1.0
101. 防災訓練参加回数/頻度	回数/頻度	1.0
102. 防災物資点検回数/頻度	回数/頻度	1.0
103. 防災計画見直し回数/頻度	回数/頻度	1.0
104. 防災意識調査実施頻度/回数	頻度/回数	1.0
105. 防災教育実施頻度/回数	頻度/回数	1.0
106. 防災情報伝達頻度/回数	頻度/回数	1.0
107. 防災意識向上頻度/回数	頻度/回数	1.0
108. 防災訓練参加頻度/回数	頻度/回数	1.0
109. 防災物資点検頻度/回数	頻度/回数	1.0
110. 防災計画見直し頻度/回数	頻度/回数	1.0
111. 防災意識調査実施回数/年数	回数/年数	1.0
112. 防災教育実施回数/年数	回数/年数	1.0
113. 防災情報伝達回数/年数	回数/年数	1.0
114. 防災意識向上回数/年数	回数/年数	1.0
11		

FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Cross-Reference to Related Applications

5 This application is a continuation of pending prior application U.S. Serial
 No. 09/661,836 filed September 14, 2000, which claims priority to U.S. Serial
 No. 60/153,892 filed September 14, 1999.

Field of the Invention

 The present application relates generally to formulations containing a
tetracycline that are useful for treating or preventing mucositis.
10 [This application claims priority to U.S.S.N. 60/153,892 filed September
 14, 1999.]

Background of the Invention

 Mucositis is a dose-limiting side effect of cancer therapy and bone
marrow transplantation and is not adequately managed by current treatment
15 (Sonis, 1993a, "Oral Complications," in: *Cancer Medicine*, pp. 2381-2388,
 Holand et al.; Eds., Lea and Febiger, Philadelphia; Sonis, 1993b, "Oral
 Complications in Cancer Therapy," In: *Principles and Practice of Oncology*, pp.
 2385-2394, De Vitta et al., Eds., J. B. Lippincott, Philadelphia). Oral mucositis
is found in almost 100% of patients receiving radiotherapy for head and neck
20 tumors, in about 40% of patients receiving chemotherapy, and in about 90% of
 children with leukemia (Sonis, 1993b, supra). Complications related to oral
mucositis, though varying in the different patient populations, generally include
pain, poor oral intake with consequent dehydration and weight loss, and
systemic infection with organisms originating in the oral cavity leading to
25 septicemia (Sonis, 1993b; U.S. patent No. 6,025,326 to Steinberg et al.).
In addition to the oral cavity, mucositis may also affect other parts of the gastro-
intestinal tract.

 A variety of approaches to the treatment of oral mucositis and associated
oral infections have been tested with limited success. For example, the use of an

Clean Copy of Amended Specification Page 1
Pursuant to 37 C.F.R. § 1.121(b)(1)(ii)

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FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Cross-Reference to Related Applications

This application is a continuation of pending prior application U.S. Serial
5 No. 09/661,836 filed September 14, 2000, which claims priority to U.S. Serial
No. 60/153,892 filed September 14, 1999.

Field of the Invention

The present application relates generally to formulations containing a
tetracycline that are useful for treating or preventing mucositis.

10

Background of the Invention

Mucositis is a dose-limiting side effect of cancer therapy and bone
marrow transplantation and is not adequately managed by current treatment
(Sonis, 1993a, "Oral Complications," in: *Cancer Medicine*, pp. 2381-2388,
Holand et al.; Eds., Lea and Febiger, Philadelphia; Sonis, 1993b, "Oral
15 Complications in Cancer Therapy," In: *Principles and Practice of Oncology*, pp.
2385-2394, De Vitta et al., Eds., J. B. Lippincott, Philadelphia). Oral mucositis
is found in almost 100% of patients receiving radiotherapy for head and neck
tumors, in about 40% of patients receiving chemotherapy, and in about 90% of
children with leukemia (Sonis, 1993b, supra). Complications related to oral
20 mucositis, though varying in the different patient populations, generally include
pain, poor oral intake with consequent dehydration and weight loss, and
systemic infection with organisms originating in the oral cavity leading to
septicemia (Sonis, 1993b; U.S. patent No. 6,025,326 to Steinberg et al.).
In addition to the oral cavity, mucositis may also affect other parts of the gastro-
25 intestinal tract.

A variety of approaches to the treatment of oral mucositis and associated
oral infections have been tested with limited success. For example, the use of an
allopurinol mouthwash, an oral sucralfate slurry, and pentoxifyline were
reported in preliminary studies to result in a decrease in mucositis. Subsequent